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REMARKS

Claims 1-6 and 11-19 are pending in the subject application. Applicants hereinabove have amended claim 1 and canceled claims 3-5, 7-10, 20-23 and 29-38, without prejudice. Accordingly, claims 1, 2, 6 and 11-19 are still pending and under examination.

Applicants maintain that the amendments to claims do not raise any issue of new matter, and that the claims, as amended, are fully supported by the specification as originally filed.

Applicants have amended claim 1 to recite the term "psoriatic arthritis" found in dependent claim 4 which is being canceled concurrently. Applicants have also amended claim 2 to recite the language "in a series of doses separated by intervals of days or weeks," and amended claim 11 to give proper claim dependency. Applicants have also canceled 7-10, 20-23 and 29-38, without prejudice, as withdrawn.

Applicants note that the Supplemental Amendment is being filed to place this application in condition for allowance, or alternatively to place claims 1, 2, 6 and 11-19 in better form for appeal. Applicants further maintain that the Supplemental Amendment satisfies the provisions of 37 C.F.R. §1.116 and M.P.E.P. §714.12, and should therefore be entered.

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The Claimed Invention

This invention provides methods for treating or preventing psoriatic arthritis in an individual in need thereof comprising co-administering methotrexate and a TNF α antagonist to said individual, in therapeutically effective amounts. In the preferred embodiment, the TNF α antagonist is an anti-TNF α antibody or antigen-binding fragment thereof.

The invention is based on applicants' *surprising discovery* that methotrexate and a TNF α antagonist behave synergistically in treating psoriatic arthritis. That is, these two agents treat psoriatic arthritis more effectively than either agent alone.

March 26, 2004 Advisory Action

On March 26, 2004, the Examiner issued an Advisory Action stating that applicants' February 4, 2004 Communication had not overcome the rejections made in the November 4, 2003 Final Office Action.

July 27, 2004 Examiner's Interview

On July 27, 2004, applicants' undersigned attorney, Alan J. Morrison, Esq. had a telephonic interview with Examiner Philip Gambel concerning the Advisory Action. Applicants wish to thank the Examiner for his time and consideration during the interview.

During the July 27, 2004 interview, applicants again maintained that the claimed invention maintains priority

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back to U.S. Serial No. 07/958,248, filed October 8, 1992, and agreed to provide charts to the Examiner in support of the October 8, 1992 priority claim for the instant application.

Also, as agreed during the July 27, 2004 interview, applicants submit Genovese, et al., Arthritis & Rheumatism, Vol. 50, Issue 5, pages 1412-1419 (2004), attached hereto as **EXHIBIT 1**. This reference provides evidence that, in treating arthritis with a combination of two drugs, one cannot reasonably predict that the combination will work better than either of the two drugs alone absent experimentation. Specifically, Genovese, et al. teaches that human patients with active rheumatoid arthritis, when treated with a combination therapy of the anti-tumor necrosis factor alpha agent etanercept and the anti-interleukin-1 agent anakinra, do not receive any additive or synergistic benefit over etanercept alone. Applicants thus maintain that Genovese, et al. provides further evidence in support of the surprising and unexpected nature of applicants' invention.

Formalities

The Examiner maintained the objection to applicants' position that the instant claims maintain priority back to U.S. Serial No. 07/958,248, filed October 8, 1992. The Examiner alleged that the filing date of the instant claims is the filing date of parent application U.S. Serial No. 08/690,775, filed August 1, 1996. Specifically, the Examiner asserted that priority application U.S. Serial No. 08/403,785 and PCT/GB94/00462 do not support the broader claims of the instant

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application, including "preventing a tumor necrosis factor-mediated disease", "tumor factor-mediated disease", "binds to one or more amino acids of hTNF α selected from the group consisting of about 87-108 and about 58-80", "cA2" and "epitope of cA2."

In response, applicants note that the claims, as amended, do not recite the phrase "preventing a tumor necrosis factor-mediated disease", or "tumor factor-mediated disease." Thus, the Examiner's objection based on these phrases is obviated.

With respect to the remaining phrases, applicants maintain that the pending claims are entitled to a priority date of October 8, 1992, the filing date of U.S. Serial No. 07/958,248 (the "'248 Application").

Under 35 U.S.C. §120, a claim in a U.S. application is entitled to the benefit of the filing date of an earlier filed U.S. application if the subject matter of the claims is disclosed in the manner provided by 35 U.S.C. §112, first paragraph, in the earlier filed application. M.P.E.P. §201.11(I). It is well settled that "[t]he subject matter of a claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." M.P.E.P. §2163.03. Furthermore, a claim is supported by the disclosure in an application "when that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." M.P.E.P. §2164.01.

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Applicants maintain that the '248 Application discloses the subject matter of amended claims 1, 2, 6 and 11-19 in the manner provided by 35 U.S.C. §112, first paragraph. Similarly, parent applications, including U.S. Serial No. 08/403,785, filed May 3, 1995 (now U.S. Patent 5,741,488, issued April 21, 1998; hereinafter referred to as the "'785 Application") and PCT International Application No. PCT/GB94/00462, filed March 10, 1994 (the "'462 Application"), provide support for the amended claims. Moreover, the '785 and '462 Applications both incorporate by reference U.S. Application 07/943,852, filed August 11, 1992, now abandoned (the "'852 Application"), which specifically discloses anti-TNF antibodies that bind to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNF α , anti-TNF antibodies that competitively inhibit binding to TNF α to monoclonal antibody cA2, and monoclonal antibody cA2. As such, the '785 and '462 Applications describe anti-TNF antibodies that bind to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNF α , anti-TNF antibodies that competitively inhibit binding of TNF α to monoclonal antibody cA2, and monoclonal antibody cA2, and these disclosures are entitled to a priority date of August 11, 1992 based on the '852 Application filing date.

Applicants point out that "TNF" and "TNF α " have been used interchangeably in the art. See, e.g., Abbas et al., Cellular and Molecular Immunology, 3rd Edition, Philadelphia: W.B. Saunders Co., pg. 258 (1997); attached hereto as EXHIBIT 2. Thus, a person skilled in the art

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would, in the context of the subject application, interpret the term "anti-TNF antibody" recited in the '248 Application to mean an anti-TNF α antibody. No evidence to the contrary has been presented. Indeed, the documents incorporated by reference at page 8, lines 13-33 of the '248 Application disclose anti-TNF α antibodies.

As agreed during the July 27, 2004 Examiner's Interview, applicants provide the charts below in support of the October 8, 1992 priority claim for the instant application.

Claims	Elements	Support in '248 Application
1	Method for treating or preventing psoriatic arthritis	Page 11, line 17 to page 12, line 4
	Co-administering methotrexate and a TNF α antagonist	Page 10, lines 6-9
2	Administered in a series of doses separated by intervals of days or weeks	Page 5, lines 4-6, and page 9, line 1 to page 10, line 5
6	TNF α antagonist prevents or inhibits TNF α synthesis or TNF α release	Page 11, lines 1-16
11	Anti-TNF α antibody or antigen-binding fragment thereof	Page 6, line 8 to page 7, line 26; page 8, lines 13-33; and page 11, lines 1-6
12	Chimeric antibody or chimeric fragment	Page 6, lines 13-17 and 21-29
	Non-human variable region specific for TNF α or an antigen-binding portion thereof and a human constant region	Page 6, lines 21-29

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Claims	Elements	Support in the '852 Application
13	SEQ ID NO:1	Page 8, lines 1-5; page 10, lines 11-19; page 15, lines 14-15; page 16, lines 15-20; page 17, line 4 to page 18, line 4; page 22, lines 26-29; Figures 13 & 15
	SEQ ID NO:2	Page 8, lines 1-5; page 10, lines 11-19; page 15, lines 14-15; page 16, lines 15-20; page 17, line 4 to page 18, line 4; page 22, lines 30-32; Figures 13 & 15
14	Chimeric antibody competitively inhibits binding of TNF α to monoclonal antibody cA2	Page 11, lines 4-7
15	Monoclonal antibody cA2	Page 11, lines 4-7; page 16, lines 25-35
16	Humanized antibody or antigen-binding fragment thereof	Page 8, lines 8-14; page 9, line 26 to page 10, line 2
17	SEQ ID NO:1	Page 8, lines 1-5; page 10, lines 11-19; page 15, lines 14-15; page 16, lines 15-20; page 17, line 4 to page 18, line 4; page 22, lines 26-29; Figures 13 & 15
	SEQ ID NO:2	Page 8, lines 1-5; page 10, lines 11-19; page 15, lines 14-15; page 16, lines 15-20; page 17, line 4 to page 18, line 4; page 22, lines 30-32; Figures 13 & 15

As shown above, the '248 and '852 Applications provide support in the manner required by 35 U.S.C. §112 for amended claims 1, 2, 6 and 11-19. Accordingly, the amended claims are entitled to a priority date of at least as early as October 8, 1992, the filing date of the '248 Application.

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The Claimed Methods are Novel

The Examiner rejected claims 1-6, 11, 13, 14 and 19 under 35 U.S.C. §102(e) as allegedly anticipated by Mak et al. (U.S. Patent No. 6,190,691; "Mak").

In response to Examiner's rejection of claims 3-5 and 19, but without conceding the correctness thereof, applicants note that these claims have been cancelled. Thus, the Examiner's rejection of these claims is now moot.

In response to the Examiner's rejection of claims 1, 2, 6 and 11, applicants respectfully traverse.

According to M.P.E.P. §706.02(b), a rejection under 35 U.S.C. §102(e) can be overcome by antedating the filing date of the reference by "[p]erfecting priority under 35 U.S.C. 119(e) and 120...by amending the specification of the application to contain a specific reference to a prior application..., and by establishing that the prior application satisfies the enablement and written description requirements of 35 U.S.C. §112, first paragraph." See also M.P.E.P. §2136.05.

As evidenced in the charts above, applicants maintain that the pending claims are entitled to a priority date of at least as early as October 8, 1992, the filing date of U.S. Serial No. 07/958,248. Applicants note that the instant application, once entitled to such priority date, antedates by almost two years the earliest claimed priority date, i.e., April 12, 1994, claimed in Mak (the entitlement to such 1994 priority date applicants do not concede). Therefore, applicants have overcome the

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\$102(e) rejection over Mak regarding claims 1, 2, 6 and 11, as amended.

In response to the Examiner's rejection of claims 13 and 14, applicants maintain that these claims are entitled to a priority date of October 8, 1992, the filing date of U.S. Serial No. 07/958,248. However, assuming *arguendo*, that claims 13, 14 and 19 are not entitled to the October 8, 1992 priority date, which applicants do not concede, these claims are also supported by the '462 Application. The '462 Application has an international filing date of March 10, 1994, and therefore, antedates the earliest priority date, i.e., April 12, 1994, claimed in Mak. Therefore, applicants have overcome the \$102(e) rejection over Mak regarding claims 13 and 14.

Alternatively, should the Examiner disagree with applicants' position that the rejections of claims 1, 2, 6, 11, 13 and/or 14 under 35 U.S.C. \$102(e) have been overcome based on priority, applicants alternatively maintain that Mak fails to anticipate the claimed invention.

Specifically, under 35 U.S.C. \$102, and as stated in M.P.E.P. \$2131.01, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (emphasis added). Hence, to anticipate the methods of claims 1, 2, 6, 11, 13 and 14, Mak would have to teach each and every element thereof.

Mak fails to do this.

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Again, claims 1, 2, 6, 11, 13 and 14, as amended, provide methods for treating or preventing psoriatic arthritis in an individual in need thereof comprising co-administering methotrexate and a TNF α antagonist to said individual, in therapeutically effective amounts. In preferred embodiments, the TNF α antagonist is an anti-TNF α antibody or antigen-binding fragment thereof.

Mak states that the pharmacological agents which are useful in this aspect of the invention are from a *broad* range of agents known in the literature for other diverse activities (column 30, lines 2-4). Indeed, from column 29, line 60 through column 43, line 2, Mak organizes the agents into several groups, such as calcium channel blockers, antianginals, cerebral, coronary and peripheral vasodilators, loop diuretics, thiazides, sodium channel antagonists, β -adrenergic agonists, neuropeptide and neurotransmitter antagonists, antihistamines and immunosuppressants, each group containing representative examples, the combined total of these examples numbering in the *hundreds*.

Although methotrexate and TNF antagonists are disclosed in Mak, there is no specific disclosure of the claimed combination of methotrexate and a TNF α antagonist, or of methotrexate and anti-TNF α antibody, to treat or prevent psoriatic arthritis. In fact, Mak only generally discloses combination therapies as evidenced by the following: "combination of occlusion and pharmacological agents" (column 53, lines 8-9; column 57, lines 65-67), "combination of pharmacological agents" (column 63, lines 15-18; column 58, lines 5-6), "anti-inflammatory

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agent...in combination with one or more different drugs" (column 55, lines 24-30) and "pharmacological agents...in combination with a penetration blocking agent" (column 60, lines 40-44).

Applicants stress that teaching a broad genus from which a specific species is claimed does not constitute disclosing the claimed species. Contrary to the Examiner's assertion that Mak discloses the claimed species, Mak actually discloses a broad genus encompassing an astronomical number of possible combination therapies, only one of which combinations is recited in the instant claims, as amended. Without Mak's specifically teaching the claimed species, one skilled in the art would not be able to envisage that species from the extremely broad statements in Mak such as "combination of pharmacological agents" or "anti-inflammatory agent...in combination with one or more different drugs."

Hence, Mak does not teach the combination of methotrexate and a TNF α antagonist recited in the amended claims, and fails to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that amended claims 1, 2, 6, 11, 13 and 14 satisfy the requirements of 35 U.S.C. §102(e).

The Claimed Methods Are Not Obvious

In the Advisory Action, the Examiner maintained the rejection of claims 1-6, 11-14 and 16-19 under 35 U.S.C.

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\$103 as allegedly unpatentable over Mak and/or Adair et al. (U.S. Patent 5,994,510; "Adair") in view of Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1338 and 2435-2437; "Merck") and Aggarwal et al. (U.S. Patent No. 5,672,347; "Aggarwal").

In response to Examiner's rejection of claims 3-5, 18 and 19, but without conceding the correctness thereof, applicants note that these claims have been cancelled. Thus, the Examiner's rejection of these claims is now moot.

In response to the Examiner's rejection of claims 1, 2, 6, 11-14, 16 and 17, applicants respectfully traverse.

Applicants again maintain that due to entitlement to a priority date of October 8, 1992, Mak is not prior art against these claims. Thus, the Examiner's rejection is obviated.

Alternatively, applicants maintain that the invention of these claims is not *prima facie* obvious.

Again, claims 1, 2, 6, 11-14, 16 and 17, as amended, provide methods for treating or preventing psoriatic arthritis in an individual in need thereof comprising co-administering methotrexate and a TNF α antagonist to said individual, in therapeutically effective amounts. In the preferred embodiment, the TNF α antagonist is an anti-TNF α antibody or antigen-binding fragment thereof.

The methods of this invention provide an unexpected advantage, e.g., inducing high clinical response rates

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for significantly longer duration in comparison with those obtained with treatment with each therapeutic modality separately. This unexpected synergistic effect is evidenced in Figures 1A, 2A, 3A, 4A, and 5A and Table 4 of the instant application. (See also, e.g., page 3, lines 18-24, Examples 1-3; particularly, page 35, lines 5-8, page 37, lines 1-3, pages 36-37 (Table 3), pages 38-39 (Table 4), page 46, line 24 through page 47, line 8 of Example 1; page 48, line 20 through page 50, line 8 of Example 2; and page 51, lines 8-32 of Example 3).

The primary references of Mak, Adair, Merck and Aggarwal have already been characterized by applicants.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest every limitation of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a *prima facie* case of obviousness because, among other things, these references fail to provide a reasonable expectation of success.

Applicants reiterate that, clearly, their experimental results are unexpected, especially when viewed in light of the teaching of Genovese, et al. As mentioned above, Genovese, et al. teaches that *human* patients with active

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rheumatoid arthritis, when treated with a combination therapy of the anti-tumor necrosis factor alpha agent etanercept and the anti-interleukin-1 agent anakinra, do not receive any additive or synergistic benefit over etanercept alone. See Genovese, et al., page 1412, Abstract, and pages 1417-1418. Genovese, et al. provides numerous reasons, such as negative interaction or overlap between the two agents, which would attribute to the unpredictable results from such combination therapies. See Genovese, et al., page 1417-1418. Although Genovese, et al. was published after the priority date of the subject application, it nevertheless underscores applicants' position that one skilled in the art would not have a basis for reasonably expecting that a combination of two agents, e.g., methotrexate and a TNF α antagonist, each known to individually treat arthritis, would result in an additive or synergistic effect absent experimentation.

Therefore, in view of the surprising nature of this invention, one of ordinary skill in the art could *not* have been able to predict, based on the cited references, whether administering both methotrexate and a TNF α antagonist to an individual would treat psoriatic arthritis *more effectively* than either agent alone. Moreover, one of ordinary skill certainly could not have reasonably expected the superior effects over either agent alone as discussed above.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1, 2, 6, 11-14, 16 and 17 over the cited references. For the same reasons,

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applicants alternatively maintain that the rejected claims would not have been obvious over these references.

In view of the above remarks, applicants maintain that claims 1, 2, 6, 11-14, 16 and 17 satisfy the requirements of 35 U.S.C. §103.

In the Advisory Action, the Examiner also maintained the rejection of claims 14 and 15 under 35 U.S.C. §103 as allegedly unpatentable over Mak and/or Adair in view of Merck and Aggarwal as applied to claims 1-6, 11-14 and 16-19 above and further in view of Le et al. (U.S. Patent No. 5,919,452; "Le").

In response to the Examiner's rejections, applicants respectfully traverse, again maintaining that Mak is not prior art against the rejected claims.

Alternatively, applicants maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

Claims 14 and 15, as amended, provide methods for treating or preventing psoriatic arthritis in an individual in need thereof comprising co-administering methotrexate and the chimeric anti-TNF α antibody cA2, or a competitive inhibitor thereof, to said individual, in therapeutically effective amounts.

The primary references of Mak, Adair, Merck, Aggarwal and Le have already been characterized by applicants.

As mentioned above, the claimed invention provides an unexpected advantage, e.g., inducing high clinical

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response rates for significantly longer duration in comparison with those obtained with treatment with each therapeutic modality separately.

Applicants reiterate that the experimental results are unexpected, especially when viewed in light of the teaching of Genovese, et al. discussed above.

Therefore, in view of the surprising nature of this invention, one of ordinary skill in the art could not have been able to predict, based on the cited references, whether administering both methotrexate and the chimeric anti-TNF α antibody cA2, or a competitive inhibitor thereof, to an individual would treat psoriatic arthritis more effectively than either agent alone. Moreover, one of ordinary skill certainly could not have reasonably expected the superior effects over either agent alone as discussed above.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 14 and 15 over the cited references. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over these references.

In view of the above remarks, applicants maintain that claims 14 and 15 satisfy the requirements of 35 U.S.C. §103.

Rejection Under Obviousness-Type Double Patenting

The Examiner rejected claims 1-6 and 11-19 under the judicially created doctrine of obviousness-type double

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patenting as allegedly unpatentable over claims 1-39 of
U.S. Patent No. 6,270,766 (the "'766 Patent").

In response to Examiner's rejection of claims 3-5, 18 and 19, but without conceding the correctness thereof, applicants note that these claims have been cancelled. Thus, the Examiner's rejection of these claims is now moot.

In response to the Examiner's rejection of claims 1, 2, 6 and 11-17, but without conceding the correctness thereof, applicants intend to file a terminal disclaimer with respect to the '766 Patent once the claims are otherwise in condition for allowance.

Provisional Rejection Based On Statutory Double Patenting

The Examiner provisionally rejected claim 1-6 and 11-19 under 35 U.S.C. §101 as allegedly claiming the same invention as that of claims 32-37, 42-50, 55-64 (or appropriate pending claims) of co-pending U.S. application Serial No. 09/921,937.

In response to Examiner's rejection of claims 3-5, 18 and 19, but without conceding the correctness thereof, applicants note that these claims have been cancelled. Thus, the Examiner's rejection of these claims is now moot.

In response to the Examiner's rejection of claims 1, 2, 6 and 11-17, applicants request that the Examiner hold this provisional rejection in abeyance until one of the two applications is allowed. Furthermore, applicants point out that subject to this application being otherwise

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allowable and co-pending application Serial No. 09/921,937 being allowed, applicants intend to cancel any claims in this application which are in fact directed to the same subject matter claimed in a different application.

Summary

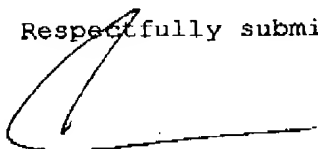
Applicants maintain that the claims pending are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

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No fee, other than the \$110.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Supplemental Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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